ACT-AD
Accelerate Cure/Treatments for Alzheimer's Disease

April 9, 2013

Nicholas Kozauer, M.D.
Clinical Team Lead
Division of Neurology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
c/o Division of Dockets Management (HFA–305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: [Docket No. FDA–2013–D–0077] Draft Guidance for Industry on Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease

Dear Dr. Kozauer,

The coalition to Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) is comprised of more than 50 national organizations representing patients, caregivers, researchers, health professionals, and other health advocates. Our mission is to support efforts to expedite the development, review, and approval of transformational therapies for Alzheimer's disease (AD). ACT-AD appreciates the opportunity to comment on the February 2013 draft "Guidance for Industry on Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease" and on behalf of the coalition, I would like to thank you for issuing this guidance at a critical time.

As you know in recent years several late-phase therapeutic development programs for AD were discontinued due to marginal or negative results. Most of these treatments were given to people with fairly advanced symptoms. With growing knowledge of Alzheimer's disease, researchers and drug developers now recognize that in order for some treatments to have the greatest impact, they must be administered earlier in the disease course. With a number of treatments for Alzheimer's disease currently in the pipeline and many more that we hope will enter, clear guidance from the FDA on what is acceptable in clinical trials targeting earlier stages of Alzheimer's disease is essential. While much of what is contained in the draft reflects views that have been expressed by FDA representatives at various meetings, including those hosted by ACT-AD, we believe the added step of codifying these views in guidance provides another layer of certainty for those seeking to carry out a clinical program in early Alzheimer's disease.

In regards to the principles for clinical outcome measures laid out Section IV of the draft guidance, we commend FDA for acknowledging the difficulty with demonstrating global/functional improvement in patients before the onset of overt dementia, and for proposing strategies to demonstrate efficacy. From the coalition's previous interaction with the agency and research community, we understand this to be an extremely challenging area, particularly when studying people in the earliest clinical stages of

disease. The strategy identified in Subsection B, to accept a measure combined to assess improvement in cognition and function, seems reasonable for people who are closest to the onset of overt dementia. The strategy is appropriately flexible because it does not limit sponsors to the use of a specific scale. The second strategy identified in Subsection C, allowing the use of a sensitive cognitive assessment tool as a primary outcome measure of efficacy for those people who have only subtle cognitive deficits, is most encouraging. With appropriate post-approval studies referenced in Subsection C, accelerated approval could for the first time serve as a viable pathway for Alzheimer's disease.

The March 28, 2013 FDA Office of Medical Policy web presentation given by you and Dr. Russell Katz provided some additional insight into specific subsets of people who you believe fall into the categories for which the two strategies in Section IV apply. Because we represent people with Alzheimer's disease, we are cognizant of the variability of the disease in individual people. We would be interested to see in the final guidance more of an emphasis on what the agency needs to be convinced that "patients" are "reliably identified" in a program looking to employ either strategy.

In Section V regarding the demonstration of disease modification, Subsection B approaches the issue of biomarkers for use as primary surrogate outcome measures. While the agency's current thinking is clear, that reliable evidence does not exist to demonstrate that a treatment effect on a biomarker ultimately predicts a clinical benefit to a person with AD, the agency also recognizes that a great deal of research has been done in this area. We do not doubt that this work will continue. The burden of providing additional evidence to make a better link between the effect on a biomarker and improved outcomes will ultimately be on the research community and industry. In order to be supportive of these efforts, FDA could go beyond mentioning the lack of "evidence-based agreement" and in the final guidance provide specificity on the types and amount of data that would be necessary to persuade the agency to consider approval of a treatment on the basis of a biomarker as a surrogate.

Lastly, since release of the draft guidance, representatives from the Division of Neurology Products have stated that it is intended to be a starting point for continued dialogue with interested stakeholders. Because of the magnitude of the problems presented by Alzheimer's disease and the number of stakeholders who have an interest in seeing better symptomatic and disease-modifying treatments for this disease, ACT-AD suggests that the agency hold a public meeting before it begins incorporating any commenter feedback into its final guidance. Such a meeting would be a useful forum for constructive stakeholder engagement, particularly after the division reviews and analyzes the comments it received during the 60-day comment period. A meeting structured with a presentation from the agency on the themes contained in the public comments, followed by a response panel including representatives from the research community, industry, patient and provider groups, and an open public comment period to close, could lead to a broadly informed and balanced final product.

We understand all too well that many of the discoveries made today will not provide relief in time to reach the millions Americans expected to suffer from the devastating effects of Alzheimer's. We want to recognize FDA for its leadership in issuing guidance that opens to door to earlier treatment of this dreaded disease and begins to clear a path for more

effective AD drug development in the future. Thank you for your careful consideration of the views expressed above and if we can be of assistance to the division as it contemplates revisions to the draft guidance, please contact Cynthia Bens on the coalition staff at cbens@agingresearch.org or (202) 293-2856.

Sincerely,

Daniel Perry
Chairman

CC. Russell Katz, M.D., Director, Division of Neurology Products, U.S. Food and Drug Administration